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## Sepsis

# Effects of ketanserin on microcirculatory alterations in septic shock: An open-label pilot study<sup>☆</sup>



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## ABSTRACT

**Introduction:** Microcirculatory alterations in sepsis are associated with increased morbidity and mortality. These alterations occur despite macrohemodynamic resuscitation. Alternative pro-microcirculatory strategies, including vasodilatory drugs, have been suggested to improve capillary blood flow. Ketanserin, a serotonin receptor antagonist, is an attractive candidate because of its vasodilatory, antithrombotic, and anti-inflammatory effects.

**Methods:** This is an open-label pilot study on the effect of ketanserin administration on microcirculatory alterations in septic shock, defined as microvascular flow index (MFI)  $\leq 2.5$  after a strict macrohemodynamic resuscitation protocol. Sidestream dark-field imaging was applied to assess the microcirculation. A stepwise incremental dose regimen was applied until an MFI  $> 2.9$ , the primary end point, was reached.

**Results:** Ten patients (Acute Physiology and Chronic Health Evaluation IV scores of 115 [100–136]) were included. Baseline MFI was 1.71 (1.31–2.32) and was significantly increasing to 2.96 (2.54–3.00;  $P = .021$ ) during the ketanserin infusion. The total ketanserin dose was 0.09 (0.08–0.13) mg/kg per patient in 60 (30–60) minutes. In 3 patients (30%), the ketanserin infusion was discontinued due to refractory hypotension.

**Conclusion:** An improvement in microcirculatory perfusion was observed during ketanserin administration in patients with septic shock after macrohemodynamic resuscitation. This finding needs further exploration in a placebo-controlled setting.

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## 1. Introduction

The microcirculation in sepsis is characterized by heterogeneous alterations in both flow and vessel density [1]. A consistent observation is the absence of a clear correlation between microcirculatory alterations and systemic hemodynamic parameters despite macrohemodynamic resuscitation [2]. Because these microcirculatory alterations are associated with increased morbidity and mortality, the microcirculation appears to be an appealing target in sepsis resuscitation [3,4]. Main aim of microcirculatory resuscitation is capillary recruitment in order to improve oxygen transport to the cells [1]. The classical paradigm is to increase perfusion pressure in order to enhance organ perfusion. However, since the introduction of in vivo microscopy at the bedside, it has become clear that augmenting blood pressure will not have beneficial effects on microcirculatory perfusion per se [5–9]. Alternatively, treatment could be directed at opening up the microcirculation by recruitment of weak microcirculatory units [10,11]. Nevertheless, studies

with different types of vasodilators have not yielded unequivocal results either [12–18]. Therefore, the search for a pro-microcirculatory resuscitation strategy continues. Ketanserin could be an attractive candidate for recruitment of the microcirculation: in addition to vasodilatory properties via serotonin (5HT) receptor 5HT<sub>2a</sub> and the adrenergic  $\alpha_1$ -receptor, ketanserin also attenuates thrombocyte aggregation and could therefore improve the microcirculation by preventing formation of occlusive microthrombi [19–22]. Furthermore, serotonin receptor antagonists are reported to have beneficial effects on cytokine profiles and leukocyte-endothelium interactions in animal sepsis models [23–25]. In cardiac surgery, ketanserin treatment lowered the incidence of endotoxemia [26]. Data on the direct effect of ketanserin on the human microcirculation are limited: in postcardiac surgery, hypertension ketanserin lowered blood pressure, without impairment of sublingual microcirculatory flow or vessel density. An improvement of digital capillary blood flow was observed in patients with Raynaud phenomenon after ketanserin treatment [27–29]. The aim of the present pilot study is to investigate the effect of a stepwise dose finding schedule of intravenous ketanserin on compromised sublingual microcirculation in patients with severe sepsis and septic shock after initial macrohemodynamic resuscitation.

<sup>☆</sup> Trial registration: NCT01329887.

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	<b>Bolus</b>	<b>Continuous infusion</b>
<i>Step 1 (T=0 minutes)</i>	0,015 mg/kg	0,03 mg/kg/hour
<i>Step 2 (T=30 minutes)</i>	0,03 mg/kg	0,06 mg/kg/hour
<i>Step 3 (T=60 minutes)</i>	0,03 mg/kg	0,09 mg/kg/hour
<i>Step 4 (T=90 minutes)</i>	0,03 mg/kg	0,12 mg/kg/hour
<b>Maximum total dose</b>	<b>0,24 mg/kg in 2 hours</b>	

**Fig. 1.** Ketanserin trial scheme. Each step consists of an intravenous bolus followed by a continuous intravenous infusion for 30 minutes. *T* indicates time; *T* = 0 minutes denotes the start of the study. Before step 1 and after each step, SDF measurements are repeated. In case of a capillary MFI  $\leq 2.5$  after a step, the ketanserin dose is increased according to this scheme.

## 2. Methods

### 2.1. Study design

This study is an open-label dose finding pilot study in 10 patients on the effect of ketanserin on sublingual microcirculatory alterations in patients 18 years or older with severe sepsis and septic shock (NCT01329887, ClinicalTrials.gov). Inclusion was characterized by 2 main criteria: (1) fulfillment of international criteria for severe sepsis or septic shock [30] and (2) persistence of microcirculatory alterations after standardized resuscitation (see below), defined as a microvascular flow index (MFI)  $\leq 2.5$  in small vessels ( $<20 \mu\text{m}$ ). Exclusion criteria were age less than 18 years, prolonged corrected QT interval, or recent oropharyngeal surgery interfering with Sidestream dark-field (SDF) measurements. The study was approved by the local ethics committee (Medical Research Ethics Committee, Medical Center Leeuwarden, the Netherlands). Written informed consent was obtained from all included patients or their legal representative in accordance with local legislation.

**Table 1**  
Baseline patient characteristics

Age (y)	63 (54–72)
Male, n (%)	5 (50)
APACHE II	30 (25–34)
Predicted mortality (APACHE II; %)	75 (65–87)
APACHE IV	115 (100–136)
Predicted mortality (APACHE IV; %)	65 (40–85)
SOFA	11 (8–14)
Sepsis type, n (%)	
Abdominal sepsis	7 (70)
Pneumosepsis	1 (10)
Necrotizing fasciitis	1 (10)
Meningitis	1 (10)
Confirmed infection, n (%)	8 (80)
LOS ICU (d)	8 (3–26)
LOS hospital (d)	24 (23–50)
ICU mortality, n (%)	5 (50)
Hospital mortality, n (%)	5 (50)
Highest arterial lactate before inclusion (mmol/L)	5.5 (4.3–7.6)
Fluid balance (0–24 h after ICU admission; mL)	5450 (3658–10450)
Steroids, n (%)	7 (70)
Mechanical ventilation, n (%)	10 (100)
PEEP (cm H <sub>2</sub> O)	12 (10–14)
F <sub>IO2</sub> (%)	50 (40–75)
Renal replacement therapy, n (%)	4 (40)

Values are median (interquartile range) unless stated otherwise. SOFA indicates Sequential Organ Failure Assessment; LOS, length of stay; PEEP, positive end-expiratory pressure; F<sub>IO2</sub>, fraction of inspired oxygen; n, number.

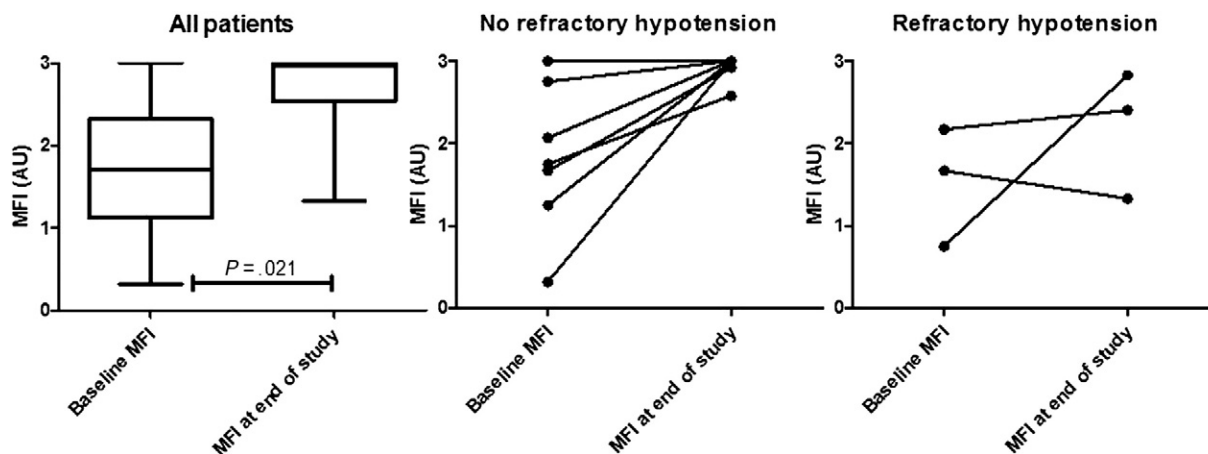
### 2.2. Sidestream dark-field imaging and analysis

Sidestream dark-field imaging and subsequent image analysis were performed in line with international consensus [31,32]. An SDF camera (MicroScan; MicroVision Medical, Amsterdam, the Netherlands) is a form of handheld intravital microscopy enabling direct visualization of the microcirculation [33]. In short, the SDF camera emits stroboscopic green light with a wavelength (530 nm) within the absorption spectrum of hemoglobin, thereby depicting erythrocytes as black cells on the screen. The area of visualization is 1 mm<sup>2</sup>.

Offline software-assisted analysis (AVA 3.0; MicroVision Medical) yields the semiquantitative MFI, ranging from 0 (no flow) to 3 (continuous flow), and percentage of perfused vessels (PPVs), providing information on convection, whereas total vessel density (TVD) and perfused vessel density (PVD) provide information on diffusion [34]. Heterogeneity index was calculated as the difference between the highest and the lowest quadrant MFI divided by the average MFI of all sublingual sites [35]. Vessels were separated into large (mostly venules) and small (mostly capillaries) using a diameter cutoff value of 20  $\mu\text{m}$ . Initial analysis of images during the screening process of patients was performed at the bedside by eyeballing MFI. Measurements were performed by a small group of dedicated researchers. The MFI was calculated as the mean for 3 different sublingual regions. Bedside assessment of MFI has good agreement with offline analysis [36]. Subsequent detailed offline analysis was performed blinded and in a randomized order to prevent coupling between images.

### 2.3. Resuscitation

Resuscitation was performed in line with a strict protocol aiming for the following resuscitation goals: a mean arterial pressure (MAP) of 60 mm Hg or greater, a mixed or central venous oxygen saturation (S(c)vo<sub>2</sub>) at least 70% and a cardiac index (CI) at least 2.5 L min<sup>-1</sup> m<sup>-2</sup>. This protocol reflects standard practice in our intensive care unit (ICU) [13,37]. Systemic hemodynamic monitoring consisted of continuous invasive monitoring of arterial blood pressure and continuous cardiac output and Svo<sub>2</sub> measurements using a pulmonary artery catheter (Vigilance; Edwards Lifesciences, Saint-Prex, Switzerland) or a pulse contour analysis system (PiCCO; Pulsion Medical Systems AG, Munich, Germany) in combination with repeated S(c)vo<sub>2</sub> measurements via a central venous line in the jugular or subclavian vein. Stepwise goal-directed protocolized resuscitation consisted of (1) repeated infusions of at least 250 mL of crystalloids, colloids, or blood products (no albumin because of high protein binding of ketanserin), until the increase in stroke volume was less than 10%. Crystalloids were the resuscitation fluids of choice; colloids and blood products were administered at the discretion of the attending physician, with



**Fig. 2.** Small-vessel (<20  $\mu\text{m}$ ) MFI at baseline and after ketanserin administration for all patients (boxplots) and for individual patients without refractory hypotension ( $n = 7$ ) and with refractory hypotension ( $n = 3$ ). AU indicates arbitrary units.

the threshold for red blood cell transfusion being a hematocrit less than 25%; (2) treatment of inadequate systemic oxygen supply (defined as  $\text{CI} < 2.5 \text{ L min}^{-1} \text{ m}^{-2}$  or  $\text{S(c)vo}_2 < 70\%$ ) with dopamine or dobutamine administered at up to  $10 \mu\text{g/kg}$  per minute and additional enoximone in case of an inadequate response to dopamine or dobutamine; and (3) treatment with norepinephrine in case of  $\text{MAP} < 60 \text{ mm Hg}$  despite the aforementioned steps. In case of hypotension despite vasopressor support, hydrocortisone at a maximum dose of  $300 \text{ mg/d}$  was administered. During the study period, therapeutic goals and resuscitation protocol remained unchanged.

#### 2.4. Screening of eligible patients

After fulfillment of the resuscitation end points, eligible patients were screened for inclusion. In case bedside SDF assessment revealed a small-vessel  $\text{MFI} \leq 2.5$ , patients were included for this study after obtaining informed consent of the patient or legal representative.

#### 2.5. Ketanserin administration and data collection

In case of a small-vessel  $\text{MFI} \leq 2.5$  after fulfillment of the above-mentioned resuscitation goals, baseline measurements (SDF, hemodynamics, blood samples) were made. After the baseline measurements, intravenous ketanserin infusion was started following the scheme in Fig. 1. Each step consisted of a ketanserin bolus, followed by a 30-minute continuous infusion, with the first step being a bolus of  $0.015 \text{ mg/kg}$  and a 30-minute continuous infusion of  $0.03 \text{ mg/kg}$  per hour. In case of hypotension ( $\text{MAP} < 60 \text{ mm Hg}$  for  $> 1$  minute) during ketanserin administration, patients were resuscitated following the standard resuscitation protocol. In case of  $\text{MAP} < 60 \text{ mm Hg}$  for more than 10 minutes or  $\text{MAP} < 50 \text{ mm Hg}$  for more than 5 minutes despite resuscitation, the ketanserin infusion was discontinued (refractory

hypotension). After each step, data on hemodynamics, applied therapy, and arterial blood gas analysis were collected. Furthermore, SDF measurements of the sublingual microcirculation were acquired. In case of a capillary  $\text{MFI} < 2.9$ , the ketanserin dose was increased following the scheme in Fig. 1, with a maximum study period of 2 hours (4 steps). The ketanserin infusion was stopped in case of an  $\text{MFI} \geq 2.9$ , refractory hypotension (see above), or after completion of all 4 steps.

#### 2.6. Statistical analysis

Because this is a pilot study, a true sample size calculation was not applicable. The sample size was in accordance with comparable previous studies [12,18]. Primary aim was to describe the changes in microcirculation observed during ketanserin administration. Secondary end points were the administered ketanserin dose and incidence of (refractory) hypotension. Whenever appropriate, a nonparametric test (Wilcoxon signed-rank test) was used to test for differences between time points. Data are presented as median (interquartile range).

### 3. Results

#### 3.1. Patients

Of 60 screened patients, 15 patients fulfilled the entry criteria of an  $\text{MFI} \leq 2.5$ . Five denied informed consent. Ten patients with Acute Physiology and Chronic Health Evaluation IV (APACHE IV) scores of 115 (100–136), Sequential Organ Failure Assessment scores of 11 (8–14), and highest lactate levels before inclusion of  $5.5 (4.3\text{--}7.9) \text{ mmol/L}$  were included after bedside confirmation of a small vessel  $\text{MFI} \leq 2.5$  (Table 1). Most patients (70%) were admitted because of abdominal sepsis. All patients but one fulfilled the criteria of septic shock, and in 80% of patients, positive cultures confirmed the presence of an infection. The ICU mortality was 50% for an APACHE IV–predicted mortality of 65% (40%–85%). The average total ketanserin dose during the study period was  $7.5 (6.2\text{--}9.8) \text{ mg}$  per patient ( $0.09 [0.08\text{--}0.13] \text{ mg/kg}$ ) in 60 (30–60) minutes. Five patients fulfilled stop criteria within 2 doses and 2 patients within 4 doses of ketanserin.

#### 3.2. Microcirculation

Before the start of the ketanserin infusion, small vessel  $\text{MFI}$  was  $1.71 (1.13\text{--}2.32)$ . During the ketanserin infusion,  $\text{MFI}$  increased to  $2.96 (2.54\text{--}3.00; P = .021)$ . In 6 of 7 patients without refractory hypotension,  $\text{MFI}$  improved to  $\text{MFI} \geq 2.9$  between T0 and the end of the ketanserin infusion. Microvascular flow index also increased in 2 of 3 patients with refractory hypotension (Fig. 2). Heterogeneity index over the course of

**Table 2**  
Microcirculatory parameters before and after ketanserin administration

	Baseline	After ketanserin	P
MFI (small vessels; AU)	1.71 (1.13–2.32)	2.96 (2.54–3.00)	.021
MFI (large vessels; AU)	2.66 (2.23–2.87)	3.00 (2.79–3.00)	.080
TVD (small vessels; $\text{mm/mm}^2$ )	23.52 (19.78–25.70)	22.31 (19.76–25.42)	.646
TVD (large vessels; $\text{mm/mm}^2$ )	3.57 (2.52–4.95)	4.76 (4.35–5.24)	.139
PVD (small vessels; $\text{mm/mm}^2$ )	18.64 (11.14–21.62)	20.49 (17.06–23.44)	.241
PVD (large vessels; $\text{mm/mm}^2$ )	3.49 (3.70–5.75)	4.76 (4.34–5.24)	.445
PPV (small vessels)	0.78 (0.55–0.90)	0.92 (0.78–0.93)	.037
Heterogeneity index (small vessels)	1.34 (0.57–2.35)	0.17 (0.00–0.49)	.021

Small vessels, vessels less than  $20 \mu\text{m}$ . AU indicates arbitrary units. Data are expressed as median (interquartile range) unless stated otherwise.

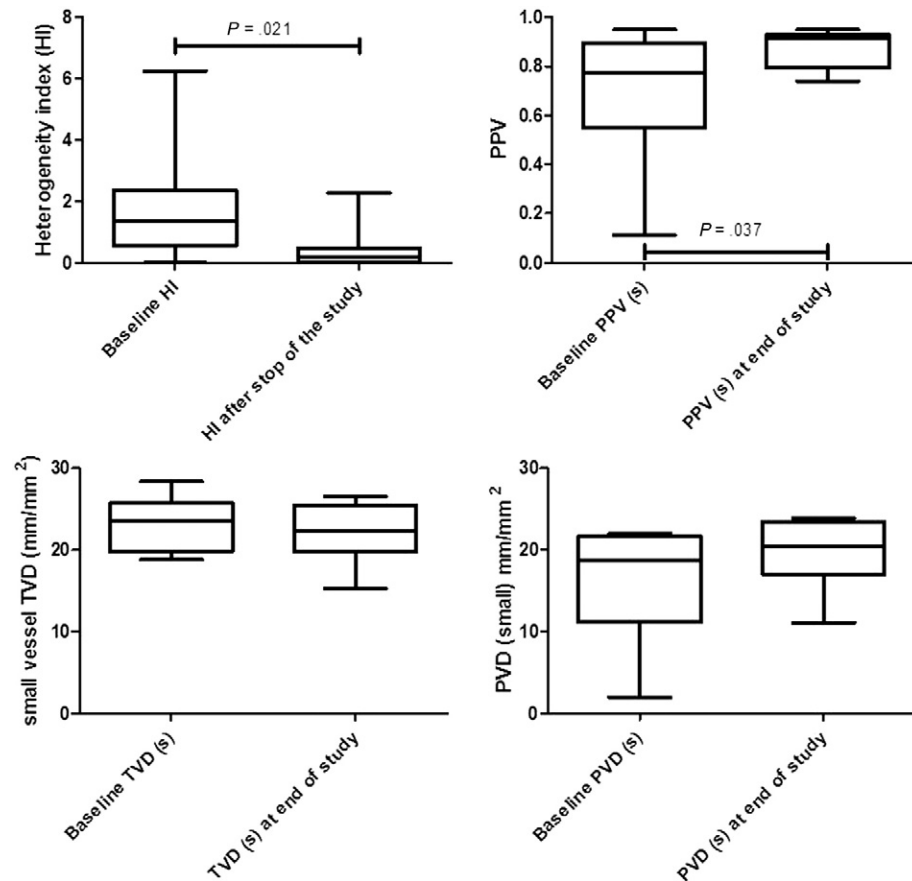


Fig. 3. Heterogeneity index (HI), PPV, TVD, and PVD for small (s) vessels ( $<20\ \mu\text{m}$ ) before and after ketanserin administration.

the study showed a significant decrease compared with baseline measurements (1.34 [0.57–2.35] vs 0.17 [0.00–0.49],  $P = .021$ ). Small vessel PPV increased (0.78 [0.55–0.90] vs 0.92 [0.78–0.93],  $P = .037$ ). Vessel densities for both small and large vessels and large vessel MFI did not show any significant changes (Table 2; Figs. 3 and 4).

### 3.3. Macrohemodynamics

Over the course of the ketanserin infusion, MAP was lowered by 6 (1–11) mm Hg leading to increases in vasopressor use in 6 patients. Average norepinephrine dosage increased from 0.19 (0.11–0.34) to 0.21 (0.19–0.36;  $P = .026$ ). In 3 patients (30%), the study was discontinued due to refractory hypotension. One of these patients had a MAP of 44 mm Hg at baseline, but remained unresponsive to further therapy. Inotropic therapy was restricted to dobutamine in 1 patient and enoximone in 2 patients. Average fluid administration during the study period was 550 (190–1275) mL. No significant changes in heart rate, CI, lactate levels, and central venous pressure (CVP) were observed, whereas  $S(c)vo_2$  significantly increased from 71% (60%–78%) to 75% (69%–81%;  $P = .024$ ). Central-to-toe temperature gradient decreased from 8.6°C (5.1–10.2°C) to 7.4°C (4.6–9.0°C;  $P = .012$ ; see Table 3 and Fig. 5 for an overview of macrohemodynamic data).

## 4. Discussion

Main finding of the present study is that microcirculatory blood flow but not vessel density increases during ketanserin administration in septic patients with a small-vessel MFI  $\leq 2.5$  at baseline. The presence of profound microvascular alterations despite macrohemodynamic resuscitation is in line with previous reports [3,13,15]. Albeit slightly

lower as predicted based on APACHE IV scores, the considerable mortality underlines the severity of disease.

At the level of the macrocirculation, ketanserin administration was accompanied by a decrease in blood pressure necessitating increases in vasopressor dose in 60% and dictating discontinuation of the study drug in 3 (30%) patients. It is difficult to determine whether this could be due to a direct (vasodilatory) effect of ketanserin or that other factors might have played a role. Ketanserin might have unmasked hypovolemia despite fulfillment of resuscitation end points in 2 of 3 patients, as illustrated by the considerable amount of fluids that was administered during the study period in most patients. Interestingly, the one patient in whom MAP was less than 60 mm Hg before the start of the ketanserin infusion managed to increase MFI to 3 despite persistence of refractory hypotension. Taken together with the significant decreases in blood pressure during the study period, this demonstrates the absence of a linear association between hypotension and microcirculatory alterations.

Ketanserin may influence microcirculatory perfusion in several ways. Ketanserin is a selective 5HT<sub>2a</sub>-receptor antagonist as well as an  $\alpha_1$ -receptor antagonist. Besides direct vasodilation by antagonism of  $\alpha_1$ -receptors, ketanserin can also induce effects on the microcirculation via the 5HT<sub>2a</sub>-receptor, 1 of 14 serotonin receptor subtypes [19,38]. Serotonin in the peripheral circulation is released by activated platelets [39]. Platelet activation appears to play a pivotal role in impairment of microcirculatory perfusion in sepsis [40,41]. Inflammatory stimuli lead to secretion of P-selectin, Von Willebrand factor, and serotonin, causing the platelets to adhere to the endothelium [42,43]. Ketanserin is known for attenuating 5HT<sub>2a</sub>-mediated platelet aggregation and might therefore prevent the formation of occlusive microthrombi [44,45].

Serotonin has a complex variety of cardiovascular effects, mediated by several subtypes of the 5HT-receptor. It is a potent vasoconstrictor by stimulating 5HT<sub>2a</sub>-mediated vasoconstriction of vascular smooth



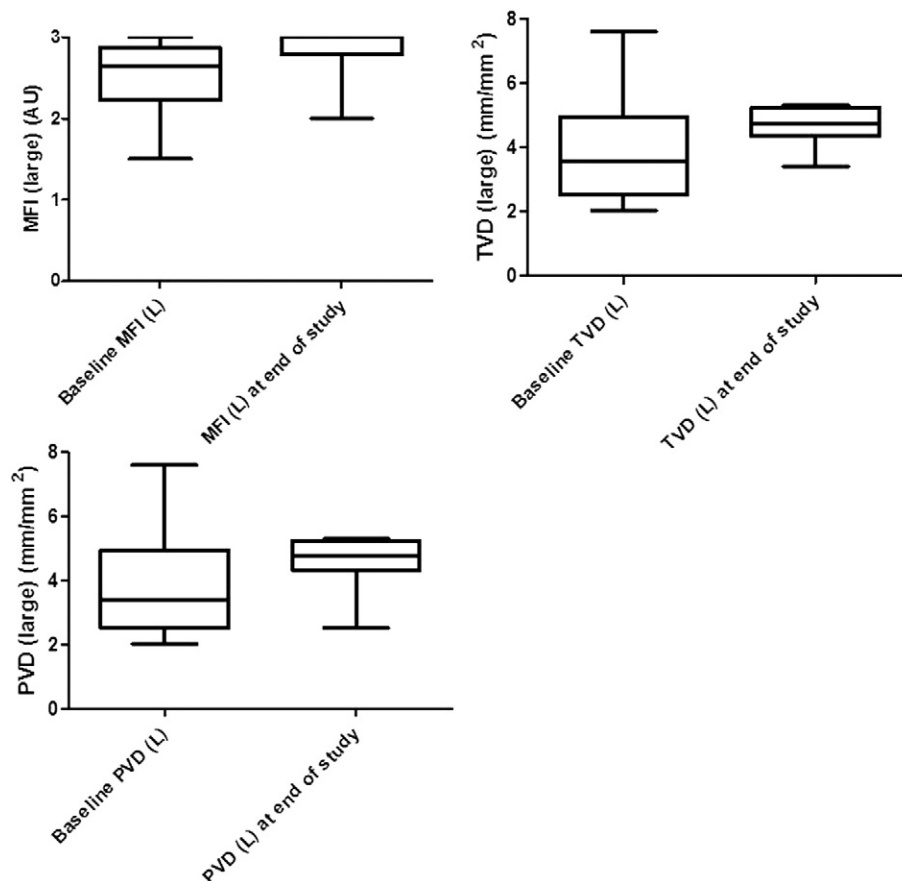


Fig. 4. Microvascular flow index, TVD, and PVD for large (L) vessels (>20  $\mu\text{m}$ ) before and after ketanserin administration.

muscle cells, whereas stimulation of the 5HT<sub>2b</sub> receptor results in endothelium dependent vasodilation by increased nitric oxide (NO) release [46]. Therefore, ketanserin can induce vasodilation by blockage of 5HT<sub>2a</sub> receptors, whereas 5HT<sub>2b</sub>-mediated vasodilation due to endothelial NO release is preserved. The resulting action of serotonin depends on the receptor subtype involved as well as the local conditions such as endothelial damage or hypoxia [46]. Under conditions of hypoxia, NO scavenging by erythrocytes can lead to profound serotonin induced vasoconstriction [47].

Data on the effects of ketanserin in human sepsis are limited. In cardiac surgery, treatment with ketanserin attenuated endotoxemia [26]. The only study applying direct in vivo microscopy of the microcirculation during ketanserin administration was performed in postcardiac

surgery hypertension. Ketanserin lowered blood pressure with a concomitant increase in large-vessel PVD, whereas small PVD and small-vessel MFI remained unchanged. This was interpreted as shunting as a result of ketanserin administration [27]. Although we did not observe signs of shunting at the level of the microcirculation in our patients, the significant increase in S(c)vo<sub>2</sub> together with stable CI and lactate levels and a lower central-to-toe temperature gradient could also indicate a shunting effect without an increase in oxygen consumption at the level of the microcirculation.

Being the first study on the effect of ketanserin on the sublingual microcirculation in septic patients, no data on potentially effective doses are available. Therefore, we decided to titrate the ketanserin dose based on microcirculatory response. Inclusion of patients with a compromised microcirculatory flow allows for a better evaluation of the effect of ketanserin: an MFI of 3 cannot be improved further. Although MFI has been validated for bedside assessment, one of the patients had an MFI of 3 at inclusion [36].

Moreover, a stepwise increase in the dose allowed for more safety with respect to inducing hypotension. Although hypotension can result from numerous causes during septic shock, administration of a vasodilator should of course be done with caution. Indeed, in 3 of 10 patients, refractory hypotension occurred. In these cases, ketanserin might have unmasked hypovolemia despite resuscitation. However, in 2 of 3 patients, hypotension persisted despite discontinuation of the ketanserin infusion.

The major limitation of this pilot study is its open-label design without a placebo group and a limited number of patients. It is difficult to determine whether the observed increase in MFI is due to the ketanserin infusion or other factors, such as timing. Our findings of improvement of microcirculatory perfusion fit in with other open-label studies on the effects of nitroglycerin and dobutamine [12,18]. However, no

**Table 3**  
Macrohemodynamic parameters, dopamine and norepinephrine dose, and lactate levels before and after ketanserin administration

	Baseline	After ketanserin	P
Heart rate (beats/min)	110 (99–130)	109 (103–131)	.683
MAP (mm Hg)	66 (60–77)	60 (53–64)	.028
Central venous pressure (mm Hg)	13 (8–15)	10 (5–16)	.160
S(c)vo <sub>2</sub> (%)	71 (60–78)	75 (69–81)	.024
CI (L min <sup>-1</sup> m <sup>-2</sup> )	3.0 (2.3–3.9)	2.9 (2.3–3.6)	.474
Central-to-toe temperature gradient (°C)	8.6 (5.1–10.2)	7.4 (4.6–9.0)	.012
Arterial lactate (mmol/L)	4.7 (2.7–6.5)	4.1 (1.8–6.5)	.609
Dopamine dose ( $\mu\text{g kg}^{-1} \text{ min}^{-1}$ )	n = 4	n = 5	.317
	5.7 (2.0–9.1)	3.3 (2.1–8.8)	
Norepinephrine dose ( $\mu\text{g kg}^{-1} \text{ min}^{-1}$ )	n = 9	n = 9	.027
	0.19 (0.11–0.34)	0.21 (0.19–0.36)	

N indicates number of patients. Data are expressed as median (interquartile range) unless stated otherwise.

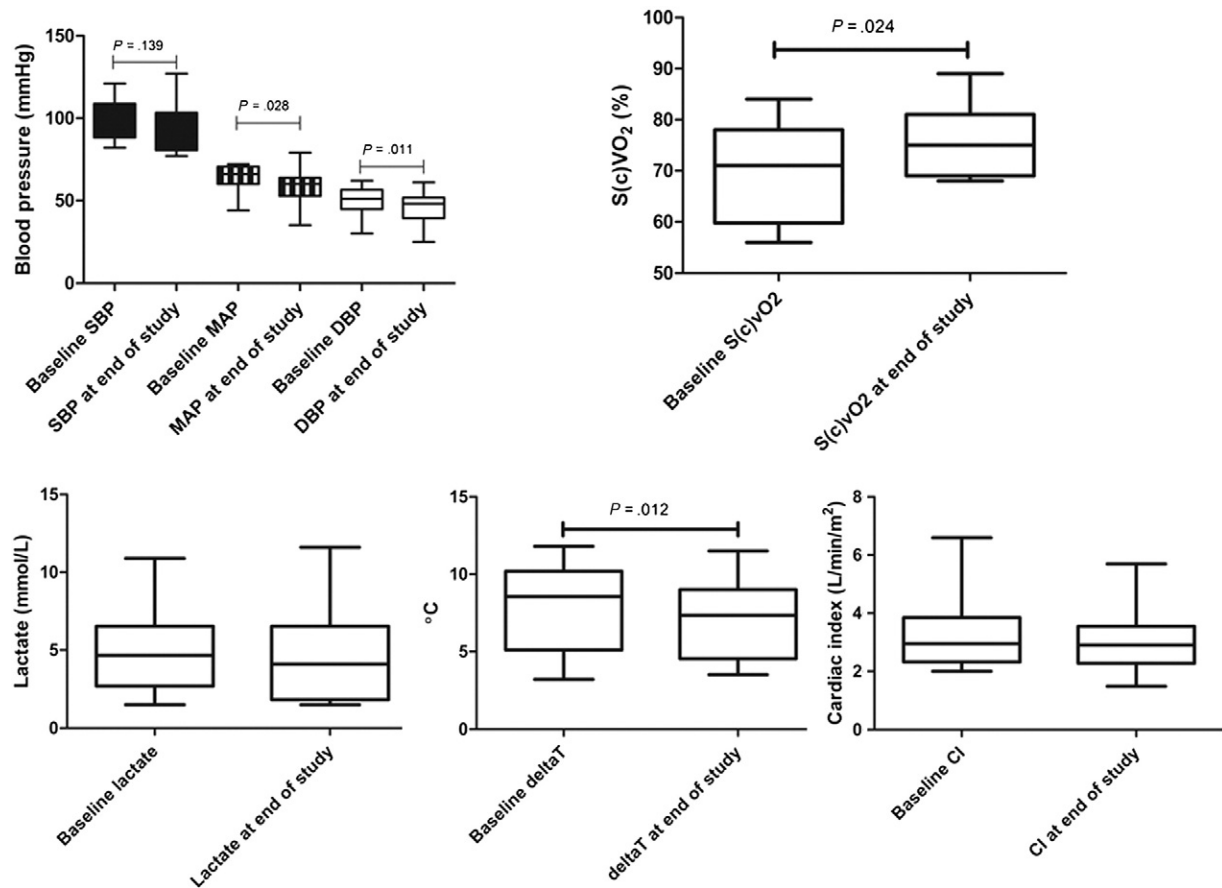


Fig. 5. Systolic blood pressure (SBP), MAP, and diastolic blood pressure (DBP), S(c)VO<sub>2</sub>, arterial lactate levels, central-to-toe temperature (deltaT), and CI before and after ketanserin administration.

significant effects could be observed when these drugs were tested in a randomized, placebo-controlled setting [13,16]. As the endothelium in sepsis remains responsive to vasodilating stimuli, maximal endogenous precapillary smooth muscle relaxation could be a factor to take into account when applying vasodilators with both nonendothelium as well as endothelium mediated properties [15,18]. This is illustrated by the blunting of any microcirculatory effects of vasodilation in the context of thoracic epidural analgesia after hypovolemic hemodilution [48]. Further experimental research is needed to elucidate the position of vasodilators in microcirculatory recruitment.

Being a pilot study, we decided to include patients with impaired microvascular flow after fulfillment of macrohemodynamic end points. Therefore, it is difficult to extrapolate our findings to patients with less severe disease. On top of that, little is known about pharmacokinetics and pharmacodynamics of ketanserin in sepsis. In nonseptic patients, ketanserin displays a nonlinear elimination with sequential half-lives of 8 minutes, 2 hours, and 14 hours, because of the partly reoxidation of one of the nonpharmacologically active metabolites to ketanserin. Reduced hepatic clearance, but not renal impairment, can influence ketanserin bioavailability, which can be of importance in our study group. Doses in our study were below the doses reported to be safe in patients with nonseptic organ impairment [19]. Spronk et al [12] reported the use of 2 mg/h of ketanserin in sepsis before administering nitroglycerin, but no information on the exact indications for starting the drug was provided.

The considerable incidence of hypotension raises questions about the safety of using this vasodilator in severely ill patients. By using a stepwise dosing protocol, we aimed to find the lowest possible dose for inducing capillary recruitment in order to minimize

chances of refractory hypotension. Of course, optimal conventional macrohemodynamic resuscitation remains the cornerstone of patient care in sepsis, and therefore, every effort should be made to avoid suboptimal macrohemodynamic resuscitation during administration of a vasodilator.

In conclusion, the observed improvement in microcirculatory perfusion during short-term ketanserin administration could fit in with the observed effects in (animal) experiments on platelet aggregation, vasodilation, inducible NO synthase, baroreceptor reflex, and cytokine profiles. Furthermore, this study provides a framework for the ketanserin dose that might lead to capillary recruitment. Although the open-label design, the small number of patients, and the considerable incidence of refractory hypotension do not allow strong conclusions, we believe that further elaboration of ketanserin-induced promotion of microcirculatory blood flow deserves exploration in a randomized placebo-controlled setting.

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